Encodes Two Isoforms with Distinct Functions in Cancers.

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Public Summary:
WNT genes encode secreted growth factors with potent stem cell activities. Deregulation of WNT expression and signaling is frequently observed in various cancers, making this signaling pathway a particularly attractive target for treatment of cancer. Here we show that a single WNT gene, WNT5A, produces two proteins that have distinct activities in human tumors. We also show that these two WNT5A isoforms may have prognostic value for survival of several cancer types.

Scientific Abstract:
WNT5A, a member of the WNT family of secreted lipid-modified glycoproteins, is a critical regulator of a host of developmental processes, including limb formation, lung morphogenesis, intestinal elongation and mammary gland development. Altered WNT5A expression has been associated with a number of cancers. Interestingly, in certain types of cancers, such as hematological malignancies and colorectal carcinoma, WNT5A is inactivated and exerts a tumor suppressive function, while in other cancers, such as melanoma and gastric carcinoma, WNT5A is overexpressed and promotes tumor progression. The mechanism by which WNT5A achieves these distinct activities in cancers is poorly understood. Here, we provide evidence that the WNT5A gene produces two protein isoforms, WNT5A-long (WNT5A-L) and WNT5A-short (WNT5A-S). Amino-terminal sequencing and a WNT5A-L specific antibody demonstrate that the mature and secreted isoforms are distinct, with WNT5A-L carrying an additional 18 N-terminal amino acids. Biochemical analysis indicates that both purified proteins are similar with respect to their stability, hydrophobicity and WNT/beta-catenin signaling activity. Nonetheless, modulation of these two WNT5A isoforms, either through ectopic expression or knockdown, demonstrates that they exert distinct activities in cancer cell lines: while WNT5A-L inhibits proliferation of tumor cell lines, WNT5A-S promotes their growth. Finally, we show that expression of these two WNT5A isoforms is altered in breast and cervix carcinomas, as well as in the most aggressive neuroblastoma tumors. In these cancers, WNT5A-L is frequently down-regulated, whereas WNT5A-S is found overexpressed in a significant fraction of tumors. Altogether, our study provides evidence that the distinct activities of WNT5A in cancer can be attributed to the production of two WNT5A isoforms.